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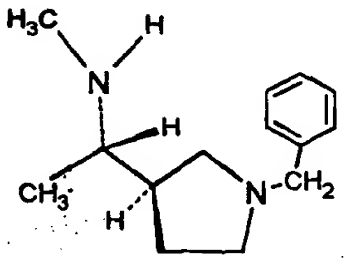
(54) Title: 3-[(1-N-METHYLAMINO)ETHYL-N-BENZYL] PYRROLIDINE MONOMETHANESULFONATE



(A-1)

• $MeSO_3H$

(57) Abstract

This invention provides a novel and useful purification step in the manufacture of a diamine pyrrolidine side chain intermediate for a quinolone antibiotic that allows production of the antibiotic in significantly greater yields and at lower costs than was previously possible. Salts, procedures and processes for preparing them, including the salt disclosed in Formula (A-1), are also disclosed.

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3-[(1'-N-METHYLAMINO')ETHYL-N-BENZYL] PYRROLIDINE MONOMETHANESULFONATE

Cross-Reference to Related Applications

This application claims the benefit of U.S. Provisional Application 60/087,194 filed May 29, 1998, and U.S. Provisional Application 60/101,848 filed September 25, 1998, the respective disclosures of which are hereby incorporated herein by reference.

Field of the Invention

This invention discloses a novel salt of a pyrrolidine intermediate used in the manufacture of a quinolone antibiotic.

Information Disclosure

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BACKGROUND OF THE INVENTION

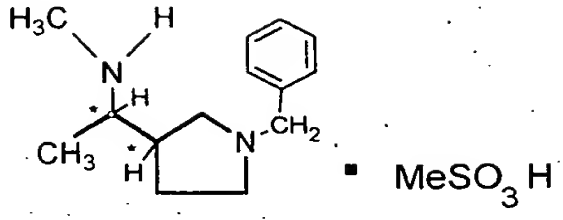
Quinolone type structures are known for their antibacterial properties, and several quinolone antibiotics (e.g. norfloxacin and ciprofloxacin) are on the market. Quinolone antibiotics may be considered as having two main structural components, the quinolone nucleus and side chains covalently bound to that nucleus. The composition of the side chain attached to the quinolone nucleus controls many of the properties of the antibiotic. Properties such as the antibiotic's potency and side effects may be strongly influenced by the structure of the side chain.

The manufacture of the side chain is a critical component in the manufacture of the quinolone antibiotic. With some quinolone antibiotics the side chain can be manufactured independently from the quinolone nucleus. This invention discloses a new method of producing a purified intermediate that can then be processed into a side chain intermediate which can be attached to a quinolone nucleus in order to produce a useful antibiotic.

Purification steps are very important in the manufacturing of pharmaceutical drugs. Every step in the manufacture of a drug requires expense in the form of operators, equipment and protocols that ensure the proper product is created. The manufacturing process and conditions must comply with both good manufacturing practices and with numerous regulations. Here we disclose a novel and useful purification step in the manufacture of a quinolone antibiotic diamine pyrrolidine side chain intermediate for a quinolone antibiotic that allows production of the antibiotic in significantly greater yields and at lower costs than was previously possible.

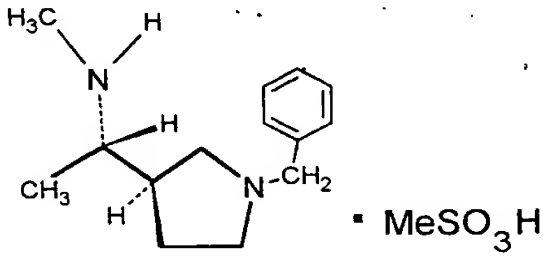
SUMMARY OF THE INVENTION

This invention comprises a compound represented by the name (3R,1'S)-3-[(1'-N-methylamino)ethyl-N-benzylpyrrolidine monomethanesulfonate and any of the compounds selected from any of the diastereomers of the salts represented by the formula below,

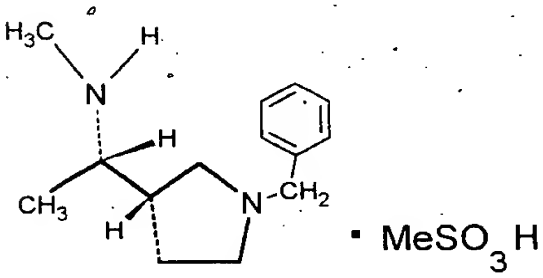


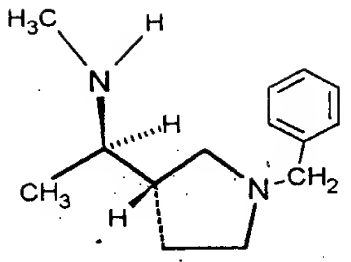
(Formula A) where * indicates an asymmetric carbon atom.

Also included are any specific diastereomers selected from any of possible diastereomers of the salt of the formula above, including the 4 diastereomers indicated below.

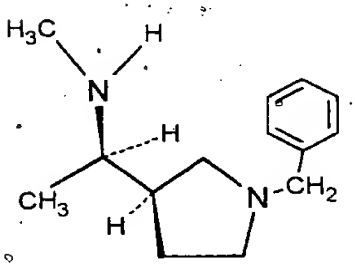


(Formula A-1)





• $MeSO_3H$



• $MeSO_3H$

Also disclosed are specific salts of formula A-1, including, a salt having the proton (1H) NMR spectra values shown below,

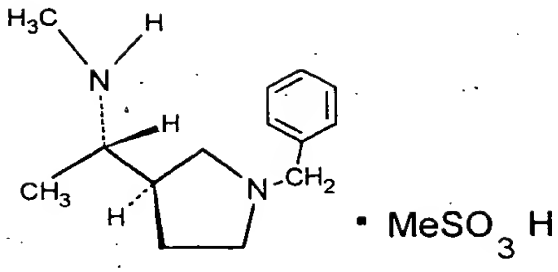
1H-NMR (CDCl3): 1.3 (d, 3H, J=6), 1.65 (m, 1H), 2.0 (m, 1H), 2.4-2.7 (m, 4H), 2.65 (s, 3H), 2.7 (s, 3H), 2.8 (m, 1H), 3.05 (t, 1H, J=9), 3.6 (d, 1H, J=13), 3.7 (d, 1H, J=13), 7.3 (m, 6H), 7.6 (bs, 1H);

A salt of formula A-1 having the carbon 13 (13C) NMR spectra values shown below,

13C-NMR (CDCl3): 13.69, 30.80, 39.31 (CH3); 26.33, 53.48, 56.86, 59.89 (CH2), 40.01, 58.37, 127.11, 128.26, 128.73 (CH), 138.23 (C)

A salt of formula A-1 having a melting point between about 91°C and about 105°C; a salt of formula A-1 having a melting point between about 91°C and about 95°C; and a salt of formula A-1 having a melting point between about 99°C and about 105°C.

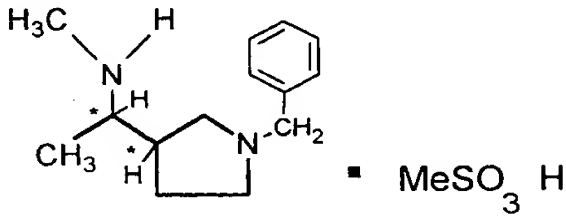
The invention also discloses procedures for producing a salt having the formula below.



(Formula A-1)

comprising the steps of

a) adding $MeSO_3H$ to any stereoisomers of the diamine shown below,



where a * indicates an asymmetric carbon atom,

b) adding sufficient solvent in which the salt is poorly soluble,

c) collecting the crystalline diamine $MeSO_3H$ salt.

In more particular, the invention describes a process where the stereoisomers of the diamine are dissolved in an anhydrous organic solvent solution before and when the $MeSO_3H$ is added; said solvent in which the salt is poorly soluble is also anhydrous and its volume is greater than the volume of the original anhydrous organic solvent (step a); the solution of salt and said solvent are heated and distilled until the volume reduction from distillation is 20% or more, with the distillation temperature being held to a maximum of about 80°C; cooling said heated and distilled mixture, with the temperature being lowered to between about 60°C to 20°C, adding previously prepared seed

salt and then cooling the resulting salt solution further by cooling to between about 40 to below -20°C, filtering said solution and collecting the crystals. Crystals can be washed in cool (about 5°C to -10°C) THF and dried again.

More particularly, the diamine can be dissolved in CH_2Cl_2 solution before and when the $MeSO_3H$ is added, and said solvent in which the salt is poorly soluble is THF and the volume of the THF is greater than the volume of original CH_2Cl_2 solvent, and said distillation temperature maximum is about 65°C, said heated and distilled mixture is cooled, with the temperature being lowered to about 45°C, and after said seed salt is added the resulting salt solution is further cooled to between about 20°C to -10°C, and then filtered, and the filtrate is then washed in cool (about 0°C to -5°C) THF, and filtered again.

Even more particularly, the heated mixture may be cooled to about 45°C for about 5 - 10 minutes, and when the seed salt is added the resulting salt solution is cooled to about 28°C for about 5 - 10 minutes, then cooled to about 20°C in about 5 min., held at 20°C for about 1 hour, then cooled to about -10 to -5°C in about 30 min. and filtered and then washed with 0°C THF and dried at about 50°C.

ADDITIONAL DESCRIPTION OF THE INVENTION AND DESCRIPTION OF THE PREFERRED EMBODIMENT(S)

Definitions

$CDCl_3$ is deuterium substituted carbon tetrachloride.

Bn is benzyl or $-CH_2$-phenyl.

"Diamine" refers to either a specific compound whose formula is shown as a $MeSO_3H$ salt in Formula A or it can refer to any of the diastereomers shown as benzylated precursors in Formulas C - G, or it may refer to any specific isomers of those compounds. The preferred isomer is shown in Formula A and is the (3R,1'S)-diastereomer.

Diastereomer refers to compound with a particular configuration. It is synonymous with enantiomer, stereoisomer, diastereoisomer, diastereomer and diasteriomer, all these terms may be used interchangeably in this document.

"NMR" or "nmr" is Nuclear Magnetic Resonance Spectroscopy.

"Prediamine" refers to the benzyl derivative precursor of the diamine, or it can refer to any of the diastereomers shown in Formulas C - G, or it may refer to any specific isomers of those compounds.

"THF" is tetrahydrofuran.

"XRD" is X-Ray Diffraction or Powder X-Ray Diffraction.

Units of Measure

°C is degree centigrade.

g is gram.

Hz is Hertz

K_i is Equilibria constant for the inhibitor.

L is Liter

M is molar or moles per liter

mg is milligram

min is minute

mHz is milliHertz

mL is milliliter

mM is milliMolar or millimoles/liter

m/z is mass per unit charge

negative numbers may be indicated with a hyphen or "-" before the number

nm is nanometers

ppm is parts per million

rpm is revolutions per minute

sec is second

'slm is standard liters per minute

µL or uL is microliter

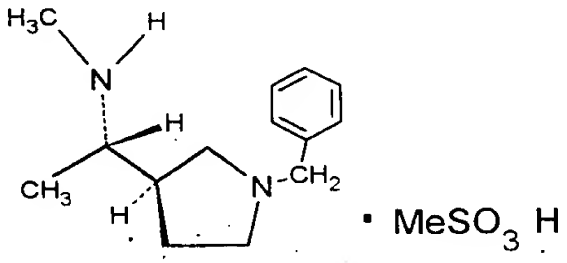
µsec is microsecond

Units of measure used should be obvious to one skilled in the art or they can be found in any most reference books.

DETAILS OF THE INVENTION

This invention describes a process for improving the purification yield of the reaction that starts with a crude prediamine mixture and produces purified diamine, shown in reaction Scheme I, below. Here, diamine is the quinolone antibiotic diamine pyrrolidine side chain intermediate, that would be coupled to the quinolone nucleus. The prediamine is prepared by an asymmetric process which produces a preponderance of the desired enantiomer. Here the (3R,1'S)-enantiomer, shown in Formula A-1, is preferred, but usually when produced it is not 100% isomerically pure. A process for the preparation of pyrrolidine side chain is disclosed in McWhorter, William W.; Fleck, Thomas J.; Pearlman, Bruce, A; "Optically Active 3-(1-(alkylamino)alkyl)pyrrolidines" PCT/US94/04548, see WO 94/26708, published 24 November 1994, applicant is Pharmacia & Upjohn Co., USA, the disclosure of which is incorporated by reference herein.

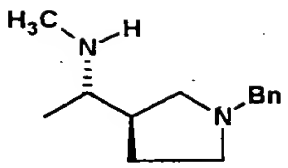
Formula A-1, or prediamine-$MeSO_3H$, which may be named, (3R,1'S)-3-[(1'-N-methylamino)ethyl-N-benzylpyrrolidine monomethanesulfonate, is shown below.



Formula A-1, or prediamine- $MeSO_3H$.

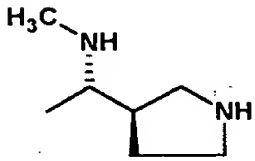
In scheme I below, the prediamine may be named, (3R,1'S)-3-[(1'-N-methylamino)ethyl-N-benzylpyrrolidine, it is converted to the diamine which may be named (3R,1'S)-3-[(1'-N-methylamino)ethylpyrrolidine.

Scheme I



Prediamine

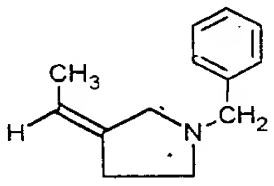
Step 1



Diamine

Typically, in the manufacture of diamine, the purity of prediamine has a large effect on the debenzylation and purification conditions that produce purified diamine.

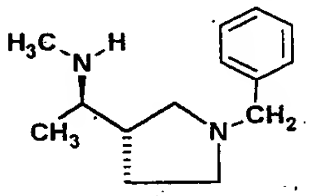
Ordinarily in the typical manufacturing process, prediamine is created in a solution that also includes byproducts or contaminates with the prediamine. Included among these byproducts are various olefinic byproducts. One such olefinic byproduct is described by Formula B, below. Such byproducts differ significantly in structure and are, therefore, relatively easy to reduce or eliminate by purification methods like distillation or pH-controlled liquid-liquid extraction.



Formula B

The typical manufacturing process also creates small amounts of undesired isomeric forms of prediamine, which are much more difficult to

remove. These include the (3S,1'R)-enantiomer, the (3R,1'R)- and (3S,1'S)-diastereomers, and the 3-(2'-N-methylamino)-regioisomers shown as Formulas C - G, below. These isomeric forms are exceedingly similar in structure and reactivity to the desired (3R,1'S)-enantiomer. Unless they are removed from the process, byproducts of this type, as well as byproducts like Formula B, can significantly reduce the purity of the diamine produced and, ultimately, the purity of the final quinolone antibiotic. Therefore, purification steps are needed which efficiently produce purified diamine.



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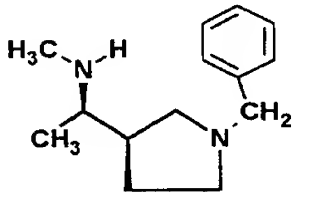

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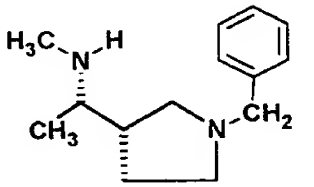

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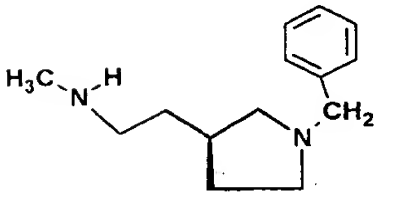

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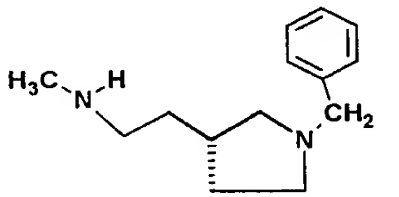


(G)

Formulas C - G

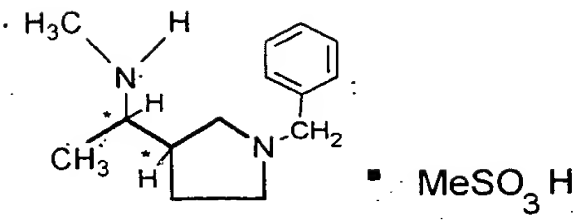
It is well known that purification by crystallization is the preferred method for removing minor contaminates which are structurally similar to the major component. Other purification methods like distillation or chromatography cannot efficiently remove isomers since they have very similar boiling points and retention characteristics. Crystallization separates such mixtures primarily on the basis of the mass of the components. A super-

saturated solution of the major component is almost always not saturated in minor components of the mixture. Thus, the crystals formed are enriched in the major component and minor components are retained in solution.

The difficulty with crystallizing the diamine is that prediamine and diamine do not crystallize in their free base forms. Previous workers in this area have reported these compounds and similar analogs and they usually suggest isolation of the compounds as oils followed by purification with inefficient chromatography. See for example, Domagala, *et. al.*, in US 5,461,165 and Hayakawa, *et. al.*, in US 5,416,222. Purification by crystallization would be a big improvement but there can be no purification of the diamine by crystallization if the prediamine does not exist in crystalline form. Discovering the conditions and materials that allow the prediamine to crystallize was key to discovering a method to produce pure diamine. Purification of prediamine via crystallization was only possible after preparing an intermediate salt with a stoichiometric amount of methanesulfonic acid ($MeSO_3H$).

This purification method was the only one shown to reduce the levels of isomeric contaminates like the (3R,1'R)-diastereomer. This corresponded to an increase in the yield of purified diamine as well as purified quinolone antibiotic.

The $MeSO_3H$ salt can be created for any of the diamine isomers (see Formula A, below) and should a process be created where a different diamine isomer was favored, then the $MeSO_3H$ salt could also be prepared for that isomer, using procedures similar to those described here for the (3R,1'S)-diastereomer. Formula A, below provides a formula that shows the two asymmetric carbon atoms in the prediamine and the covalent bonds are shown as solid lines. Other formula, such as Formula A-1, show the orientation of the relevant covalent bonds, with a dotted line indicating the bond is down, into the paper and a solid wedge shaped line indicating the bond is up out of the paper. See, Formula A-1, further below.



Formula A, above, where an " * " indicates an asymmetric carbon atom.

Crystal forms and purity.

It is possible for the purified diamine to exist in different crystal forms. The form of the crystal can vary depending upon very slight differences in manufacture. The rate of heating or cooling, the presence of impurities, the solvents used, temperature, pressure, humidity, even gravity as well as a host of other factors can all affect crystal formation. These factors can also affect melting points of crystals. An impurity in a crystal and/or the precise form of the crystal can all affect at what temperature or range of temperatures a crystal will melt.

Here we have created several crystal forms of the desired crystals and provided data to show both proton placements (NMR data) and crystal form structure (XRD data). These examples are intended to illustrate a few of the possible crystal forms and compositions possible.

The following example shows one method of making one diasteriomer of Prediamine-$MeSO_3H$ salt using prediamine which had the olefinic contaminates (like in Formula B) already removed by pH-controlled extraction. However, the process has been shown to also be effective when using typical, crude prediamine. This example is intended to illustrate and not limit the invention described above. One skilled in the art would be expected to make obvious variations and insubstantial changes from the specific conditions provided below.

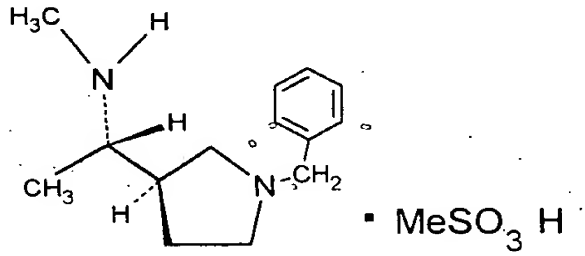
Experimental for purification of prediamine via $MeSO_3H$ salt

To a solution of partially purified prediamine, purified via pH 8 and pH 12 extractions (15.0 g, about 67.8 mmol, GC 98.7 area %, 1.0% (3R,1'R)-

diastereomer), in CH_2Cl_2 (70 ml) at 0-2°C, slowly add $MeSO_3H$ 6.67 g, 4.50 ml, 69.4 mmol, about 1.02 eq) to maintain 1-8°C (over 7 min). Add THF (anhydrous and stabilized, 150 ml) at 0-10°C (25 min). Distill to 90 ml total volume atmospherically (135 min, max pot temp 65°C). Cool to 45°C (10 min) and seed with previously made salt. Crystals form 2 min later at 40°C. Cool to 28°C (8 min) before applying cold H_2O bath. Cool to 20°C (5 min) and hold 1 hr. Cool with ice-salt bath to -10 to 0°C (30 min, -8°C) and filter. Wash with cold THF (0°C, 2 x 22 ml). Dry overnight in vacuum oven at 50°C to give crystals (18.95 g, GC 99% with 0.5% (3R,1'R)-diastereomer, about 89% of theory).

Dissolve a portion of the salt (18.0 g) in CH_2Cl_2 (90 ml) and stir with H_2O (90 ml) while adding 50% aqueous NaOH dropwise to pH 11.8-12 (2.3 ml from pH 7.8 to 11.9). Allow phases to separate, remove the lower CH_2Cl_2 phase, and extract the aqueous phase with CH_2Cl_2 (90 ml, pH still 12). Combine the two CH_2Cl_2 phases and remove solvent by rotovap and high-vacuum pump to give an oil (12.3 g, about 98% recovery). This sample was dissolved in MeOH and hydrogenated to diamine (6.89 g, GC 98% area with 0.5% (3R,1'R)-diastereomer, 99% chemical yield).

The resulting salt has the formula of Formula A-1, or prediamine-$MeSO_3H$, shown below.



Formula A-1, or prediamine- $MeSO_3H$.

(3R,1'S)-3-[(1'-N-methylamino)ethyl-N-benzylpyrrolidine monomethanesulfonate

The formation of a prediamine- $MeSO_3H$ salt can provide an easy method of producing large amounts of relatively pure diamine.

Confirmation of the structure of Formula A-1 by NMR spectroscopy

Nuclear Magnetic Resonance (NMR) spectroscopy was used to confirm the structure of Formula A. Both proton and 13C NMRs were performed. The equipment parameters and spectra and interpretation are provided here.

NMR data were recorded on a Bruker AMX300 operating at 300.13 MHz for the observation of 1H and 75.40 MHz for the observation of 13C. Samples were dissolved in, and internally referenced to, CDCl3 (1H, d = 7.26; 13C, d = 77.0). One dimensional NMR data were recorded as a 32k complex point data table with a 10,600 Hz sweep width for proton and 20,800 Hz sweep width for carbon. The number of transients and various pulse widths are listed in the appropriate figures. 1H experiments were processed with gaussian multiplication and 13C with a 2 Hz exponential multiplication prior to fourier transformation. The spectral data and interpretation provided follow standard abbreviations - d is doublet, m is multiplet, s is singlet, t is triplet, H is hydrogen, J is coupling constant in hertz. The values provided are chemical shifts in ppm (parts per million) from the reference peak.

Proton NMR.

Data Parameters: EXPNO is 11, PROCNO is 1.

Acquisition Parameters: SOLVENT is CDCl3, AQ is 1.3271240 sec, FIDRES is 0.376760 Hz, DW is 81.0 µsec., RG is 4096, NUCLEUS is 1H, HL1 is 1 dB, D1 is 3.0 sec., P1 is 10.3 µsec., DE is 101.3 µsec., SFO1 is 300.1351620 MHz, SWH is 6172.84 Hz, TD is 16384, NS is 16 , DS is 2.

Processing parameters: SI is 16384, SF is 300.1333581 MHz, WDW is GM, SSB is 0, LB is -0.30 Hz, GB is 0.15, PC is 3.00.

Proton NMR spectra and interpretation:

1H-NMR (CDCl3): 1.3 (d, 3H, J=6), 1.65 (m, 1H), 2.0 (m, 1H), 2.4-2.7 (m, 4H), 2.65 (s, 3H), 2.7 (s, 3H), 2.8 (m, 1H), 3.05 (t, 1H, J=9), 3.6 (d, 1H, J=13), 3.7 (d, 1H, J=13), 7.3 (m, 6H), 7.6 (bs, 1H);

13C NMR.

Data Parameters: EXPNO is 14, PROCNO is 1.

Acquisition Parameters: SOLVENT is CDC13, AQ is 0.327700 sec, FIDRES is 1.525879 Hz, DW is 20.0 μsec., RG is 4096, NUCLEUS is 13C, HL1 is 1 dB, D1 is 1.0 sec., S1 is 1dB, P3 is 9.0 μsec., SFO2 is 300.1346670 MHz, D2 is 0.0035714 sec., P4 is 18.0 μsec., P1 is 7.0 μsec., P2 is 14.0 μsec., S2 is 22 dB, DE is 25.0 μsec., SF01 is 75.4753020 MHz, SWH is 25000.00 Hz, TD is 16384, P31 is 100.0 μsec., NS is 256, DS is 4.

Processing parameters: SI is 16384, SF is 75.4685977 MHz, WDW is EM, SSB is 0, LB is 2.00 Hz, GB is 0, PC is 1.40.

13C-NMR spectra and interpretation:

13C-NMR (CDCl3): 13.69, 30.80, 39.31 (CH3); 26.33, 53.48, 56.86, 59.89 (CH2), 40.01, 58.37, 127.11, 128.26, 128.73 (CH), 138.23 (C)

Confirmation of the structure of Formula A-1 by XRD spectroscopy

A Rigaku DMAX-A X-ray diffractometer is employed for the acquisition of the powder XRD patterns. The instrument is operated with the copper K-L_3 radiation at 1.5406 Å. The major instrumental parameters are set as follows: 40 KV voltage, 30 mA current, beam aperture of 1° and detector aperture (receiving slit) of 0.30°. Patterns are scanned over the range of 3-40° two-theta angles with a scan rate of 1.5° two-theta/min (step size of 0.05° and counting time at 2 second/step). Samples are ground to fine powders and packed into an aluminum tray. Complete description of the parameters and abbreviations used below may be found in either the operations manual for the Rigaku DMAX-A X-ray diffractometer, or they may be found in most XRD manuals.

Peak Reports for three different crystals are provided here. The first report, below, shows the spectra for a crystal with a melting point between about 99 and 105 °C.

Number 1. Area Sum: 8308.309

STD	Center X	Height	Width	Area	Qty	Name
0	5.834918	1092.0131	.8751047	224.19034	0	5.83
0	9.9110054	383.73329	.8273052	104.87254	0	9.91
0	11.13072	451.63211	.585815	94.732384	0	11.13

	0	11.69375	528.70474	.666675	114.14881	0	11.69
	0	14.795333	1797.9825	1.455302	479.67671	0	14.79
	0	15.921212	1476.2741	.951913	363.07695	0	15.92
	0	17.471698	1855.8032	1.323417	677.98383	0	17.47
5	0	18.475686	410.45285	.503866	75.167063	0	18.47
	0	19.023329	3268.1195	1.237003	971.86381	0	19.02
	0	19.219853	873.31139	.261395	152.85561	0	19.22
	0	19.605024	2792.0912	.424057	540.56151	0	19.6
	0	19.975194	357.01175	.541624	-51.32979	0	19.97
10	0	21.241494	2645.4923	1.175444	1083.6633	0	21.24
	0	22.891667	1559.2777	1.301086	606.35257	0	22.89
	0	23.521112	913.09385	.494843	222.95287	0	23.52
	0	24.133978	1019.5988	.554393	345.74773	0	24.13
	0	24.508086	1264.6217	.392158	336.29395	0	24.51
15	0	25.017281	1913.1805	1.519106	632.57096	0	25.02
	0	25.401105	215.86944	.817443	248.49867	0	25.4
	0	25.918957	-87.41223	1.569454	-370.6186	0	25.92
	0	26.815625	132.78142	.462531	31.495602	0	26.81
	0	27.092949	123.79176	.690996	42.244557	0	27.09
20	0	28.224462	600.42504	.859375	193.27808	0	28.22
	0	28.830992	610.87875	.608551	167.68869	0	28.83
	0	29.488636	324.3707	.623618	97.977263	0	29.49
	0	30.005232	222.75713	.582108	70.931509	0	30
	0	31.122761	255.15629	.854026	79.714945	0	31.12
25	0	32.5	92.051473	.582163	29.329946	0	32.5
	0	33.162097	266.93974	.52954	61.269216	0	33.16
	0	33.745714	71.357752	.569382	20.886694	0	33.74
	0	34.668382	146.45223	.992	65.5167	0	34.67
	0	35.547222	255.87001	.609394	68.453135	0	35.55
30	0	35.984862	156.83937	.577744	36.357722	0	35.98
	0	37.268038	242.6646	.917453	94.268565	0	37.27

0	37.880357	75.850116	.463806	16.364475	0	37.88
0	38.438983	1012.3131	1.606297	350.42475	0	38.44
0	39.473034	119.39596	.555893	28.845653	0	39.47

The second report, below, shows the spectra for a crystal with a melting point between about 99 and 105°C.

Number 2. Area Sum: 13396.29

STD	Center X	Height	Width	Area	Qty	Name
0	5.9715556	7027.6799	1.3933285	1240.5507	0	5.97
0	9.8595943	802.23455	.95033977	157.99408	0	9.86
0	11.128762	962.72309	.83826671	185.32174	0	11.13
0	11.933489	5107.8936	1.1434835	843.2251	0	11.93
0	12.979861	248.5398	.59978733	41.478462	0	12.98
0	14.770327	797.52601	.99394451	164.05737	0	14.77
0	15.223529	158.05241	.49794698	29.780324	0	15.22
0	16.608459	1287.2919	1.0963857	267.2659	0	16.61
0	17.657398	4447.2803	.72198886	1065.9162	0	17.66
0	17.927192	4573.0339	.54387841	819.07926	0	17.93
0	18.884714	4399.7459	.62235323	916.47831	0	18.88
0	19.085128	6096.8224	.50971719	1123.0525	0	19.08
0	19.810571	470.83092	.4129033	60.143712	0	19.81
0	20.200498	4813.3296	.95528902	1137.7599	0	20.2
0	20.964015	186.93076	.40539918	28.206431	0	20.96
0	21.827907	1762.838	.77977651	420.34597	0	21.83
0	22.271059	1275.6447	.58514569	314.27325	0	22.27
0	22.990567	1508.8252	.73054087	315.12441	0	22.99
0	24.015809	5758.6184	1.3634189	1336.4861	0	24.01
0	24.444188	599.2165	.84461837	425.62015	0	24.44
0	25.029239	927.12006	.66213916	207.90402	0	25.03
0	25.818684	1492.6358	.89375199	428.21817	0	25.82
0	26.035822	177.30743	.28641852	26.096782	0	26.03
0	26.413524	4.2728519	.38634407	1.1535085	0	26.41

	0	27.394792	926.09227	.76494323	209.49965	0	27.39
	0	28.655916	1440.6638	.87687014	406.14477	0	28.65
	0	30.127184	703.33693	1.1222087	231.53941	0	30.13
	0	30.818846	142.60067	.52772255	25.706841	0	30.82
5	0	31.613529	783.3234	.80394348	186.49975	0	31.61
	0	32.213596	374.77607	.80186508	108.73435	0	32.21
	0	33.170833	391	.94545542	125.11446	0	33.17
	0	35.032308	76.362971	.40026442	15.120593	0	35.03
	0	35.577371	451.05412	1.2308229	187.78989	0	35.58
10	0	36.349167	360.65748	.6245618	75.278669	0	36.35
	0	38.433815	895.70864	.89174144	216.18376	0	38.43
	0	39.676202	179.07396	.65	53.15	0	39.68

The third report, below, shows the spectra for a crystal with a melting point between about 91 and 95°C.

15 Number 3. Area Sum: 9154.595

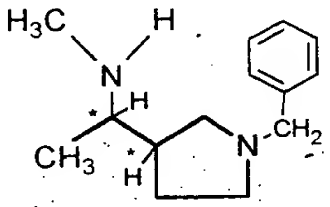
	STD	Center X	Height	Width	Area	Qty	Name
	0	5.9153846	944.01017	1.0937917	271.89777	0	5.91
	0	9.8864754	424.13142	.73957126	82.445475	0	9.89
	0	11.137689	458.44108	.72857206	90.561068	0	11.14
20	0	11.736436	295.01043	.42062792	57.883083	0	11.74
	0	11.912097	270.45386	.35773856	45.651294	0	11.91
	0	14.799397	1473.0095	1.0211427	288.99874	0	14.8
	0	15.929309	908.03285	.76254095	197.24495	0	15.93
	0	16.631835	775.74021	.71458333	184.31585	0	16.63
25	0	17.518764	1458.3208	.69189122	377.16544	0	17.52
	0	17.681298	1401.3277	.17642639	223.97892	0	17.68
	0	17.928364	1766.818	.42884906	384.66641	0	17.93
	0	18.493333	198.697	.40320057	32.965388	0	18.49
	0	19.06505	3318.8726	1.1921022	1589.6955	0	19.06
30	0	19.617385	2315.4976	.48113491	671.13181	0	19.62
	0	20.19373	2687.976	.8195737	842.38561	0	20.19

	0	20.571512	164.77539	.25451639	23.855266	0	20.57
	0	21.266521	1431.421	.82361901	613.48087	0	21.27
	0	21.845448	1036.8835	.52982799	258.09355	0	21.84
	0	22.2898	786.16844	.46039375	203.43032	0	22.29
5	0	22.922488	979.30254	.74892663	360.64567	0	22.92
	0	23.529706	438.59226	.41670751	110.79993	0	23.53
	0	24.121519	948.97611	.60244684	379.03961	0	24.12
	0	24.48561	1424.7514	.43338209	349.13472	0	24.48
	0	25.039211	1521.3687	.86442201	432.59769	0	25.04
10	0	25.418595	201.42547	.28827287	28.952083	0	25.42
	0	27.412277	463	.69236495	122.18741	0	27.41
	0	28.263393	320.80197	.491224	89.646156	0	28.26
	0	28.690079	403.3547	.72602709	151.88305	0	28.69
	0	29.518939	176.73902	.50940204	50.783171	0	29.52
15	0	29.990476	199.61121	.68674462	83.839193	0	29.99
	0	31.163587	92.31139	.50992405	19.136831	0	31.16
	0	32.219697	107.07185	.61296813	26.201445	0	32.22
	0	33.177174	302.24777	1.2885351	86.682518	0	33.18
	0	33.7375	59.417303	.56476314	20.061035	0	33.74
20	0	35.530078	231.34934	.705873	58.259443	0	35.53
	0	37.27931	108.05567	.78690464	30.966579	0	37.28
	0	38.444396	1006.0711	1.0134273	280.65145	0	38.44
	0	39.670588	88.837647	.9375	33.279688	0	39.67

Claims:

1. A composition comprising the compound represented by the name (3R,1'S)-3-[(1'-N-methylamino)ethyl-N-benzylpyrrolidine monomethanesulfonate.

2. A composition comprising a compound selected from any of the diastereomers of the salts represented by the formula

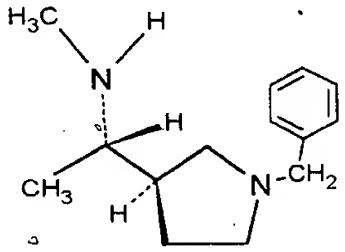


$\cdot MeSO_3H$

(Formula A)

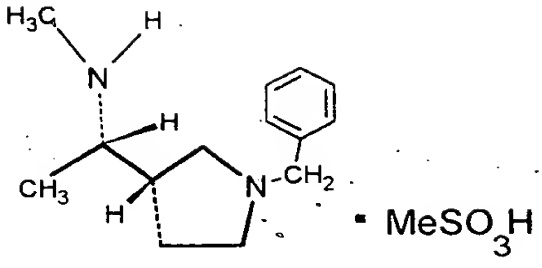
where * indicates an asymmetric carbon atom.

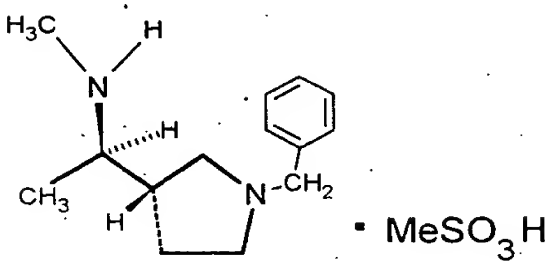
3. A composition comprising a specific diastereomer selected from any of four possible diastereomers of the salt of claim 2, where the four possible diastereomers are indicated below:

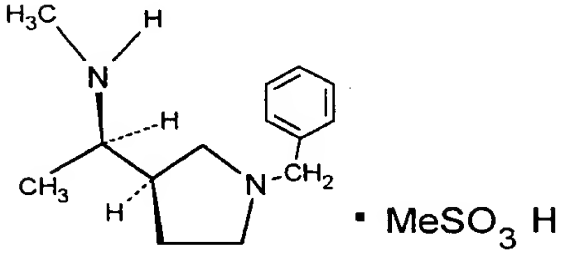


$\cdot MeSO_3H$

(Formula A-1)

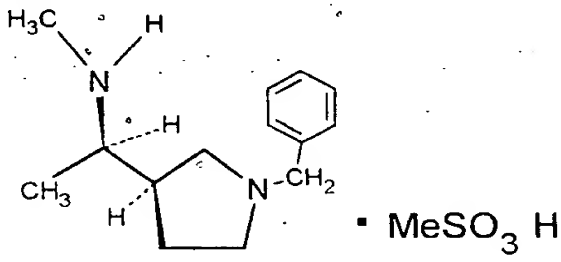






5

4. A composition comprising a specific diastereomer selected from the salts of claim 3, said diastereomer having the formula



(Formula A-1)

5. A composition comprising the salt of claim 4, said salt having the proton (1H) NMR spectra values shown below:

1H-NMR (CDCl3): 1.3 (d, 3H, J=6), 1.65 (m, 1H), 2.0 (m, 1H), 2.4-2.7 (m, 4H), 2.65 (s, 3H), 2.7 (s, 3H), 2.8 (m, 1H), 3.05 (t, 1H, J=9), 3.6 (d, 1H, J=13), 3.7 (d, 1H, J=13), 7.3 (m, 6H), 7.6 (bs, 1H);

6. A composition comprising the salt of claim 4, said salt having the carbon 13 (13C) NMR spectra values shown below:

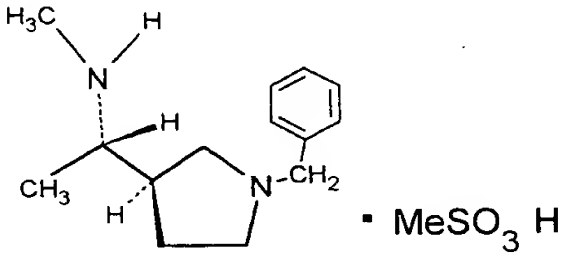
13C-NMR (CDCl3): 13.69, 30.80, 39.31 (CH3); 26.33, 53.48, 56.86, 59.89 (CH2), 40.01, 58.37, 127.11, 128.26, 128.73 (CH), 138.23 (C).

7. A composition comprising the salt of claim 4, said salt having a melting point between about 91°C and about 105°C.

8. A composition comprising the salt of claim 6, said salt having a melting point between about 91°C and about 95°C.

9. A composition comprising the salt of claim 6, said salt having a melting point between about 99°C and about 105°C.

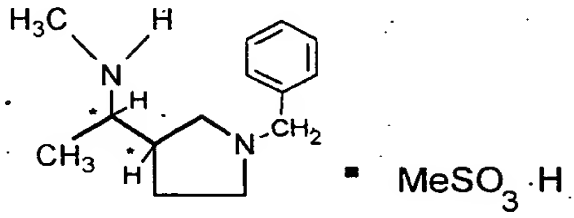
10. A process for producing the salt having the formula



(Formula A-1)

comprising the steps of

a) adding $MeSO_3H$ to any stereoisomers of the diamine shown below,



where a * indicates an asymmetric carbon atom;

b) adding sufficient solvent in which the salt is poorly soluble;

c) collecting the crystalline diamine $MeSO_3H$ salt.

11. The process of claim 10 comprising the steps of:

a) in step a of claim 10, dissolving the stereoisomers of the diamine in an anhydrous organic solvent solution before and when the $MeSO_3H$ is added;

b) in step b of claim 10, said solvent in which the salt is poorly soluble is anhydrous and its volume is greater than the volume of the original anhydrous organic solvent (step a of the present claim);

c) after step b of claim 10, heating and distilling the solution of salt and said solvent until the volume reduction from distillation is 20% or more, and holding the distillation temperature to a maximum of about 80°C;

d) after step c of the present claim, cooling said heated and distilled mixture, and lowering the temperature to between about 60°C to 20°C; and

e) after step d of the present claim, adding previously prepared seed salt and then cooling the resulting salt solution further by cooling to between about 40 to below -20°C, filtering said solution, and collecting the crystals.

12. The process of claim 11, comprising the steps, after step (e) of claim 11, of washing the crystals in cool (about 5°C to -10°C) THF after the crystals are filtered and drying the washed crystals.

13. The process of claim 12 wherein:

said solvent in which the diamine is dissolved in before and when the $MeSO_3H$ is added is CH_2Cl_2;

said solvent in which the salt is poorly soluble is THF and the volume of the THF is greater than the volume of original CH_2Cl_2 solvent; and

said distillation temperature maximum is about 65°C,

said process comprising the steps of:

cooling said heated and distilled mixture to a temperature of about 45°C;

after said seed salt is added, further cooling the resulting salt solution to between about 20°C to -10°C, and then filtering the solution; and

after the crystals are filtered, washing the crystals in cool (about 0°C to -5°C) THF, and then filtering the crystals again.

14. The process of claim 13 comprising the steps of:

cooling said heated mixture to about 45°C for about 5 to 10 minutes;

adding said seed salt and cooling the resulting salt solution to about 28°C for about 5 to 10 minutes, then cooling the solution to about 20°C in

about 5 min., holding the solution at 20°C for about 1 hour, then cooling the solution to about -10 to -5°C in about 30 min.; and

filtering and then washing the crystals with 0°C THF and drying the crystals at about 50°C.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11739

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/09

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 207 420 A (DAIICHI SEIYAKU CO., LTD., JAPAN) 7 January 1987 (1987-01-07) page 35 -page 36; example 25	1,2
A	WO 94 26708 A (UPJOHN CO., USA) 24 November 1994 (1994-11-24) cited in the application abstract; claim 1 page 51 -page 54	1,2
P,A	EP 0 855 390 A (TAKASAGO INTERNATIONAL CORP., JAPAN) 29 July 1998 (1998-07-29) abstract; claim 1 page 14; example 19	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 October 1999	19/10/1999

Name and mailing address of the ISA	Authorized officer
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Information on patent family members

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PCT/US 99/11739

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